

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
14 November 2002 (14.11.2002)

PCT

(10) International Publication Number
WO 02/090326 A1

(51) International Patent Classification⁷: C07D 207/09, 207/14, A61K 31/402

(21) International Application Number: PCT/EP02/04802

(22) International Filing Date: 2 May 2002 (02.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 0110901.6 2 May 2001 (02.05.2001) GB

(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): RAMI, Harshad, Kantilal [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). THOMPSON, Mervyn [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WYMAN, Paul, Adrian [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: RUTTER, Keith; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/090326 A1

(54) Title: HETEROCYCLIC UREAS, THEIR PREPARATION AND THEIR USE AS VANILLOID RECEPTOR ANTAGONISTS

(57) Abstract: The invention relates to compounds of formula (I) having Vanilloid Receptor (VR1) antagonist activity, processes for their preparation, to compositions containing them and to their use in the treatment of various disorders.

HETEROCYCLIC UREAS, THEIR PREPARATION AND THEIR USE
AS VANILLOID RECEPTOR ANTAGONISTS

This invention relates to novel compounds and in particular to urea derivatives
5 having pharmacological activity, processes for their preparation, to compositions
containing them and to their use in medicine.

Vanilloids are a class of natural and synthetic compounds which are characterised
by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally
equivalent group. Vanilloid Receptor (VR1), whose function is modulated by such
10 compounds, has been widely studied and is extensively reviewed by Szallasi and Blumberg
(The American Society for Pharmacology and Experimental Therapeutics, 1999, Vol. 51,
No. 2.).

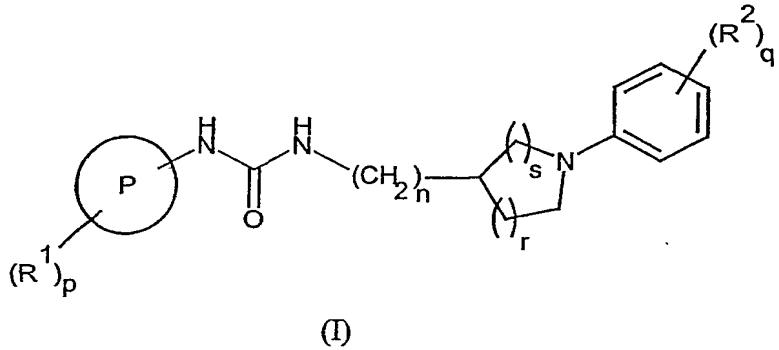
A wide variety of Vanilloid compounds of different structures are known in the
art, for example those disclosed in EP 347000, EP 401903, GB 2226313 and WO
15 92/09285. Particularly notable examples of vanilloid compounds or vanilloid receptor
modulators are capsaicin, namely *trans* 8-methyl-N-vanillyl-6-nonamide, isolated from
the pepper plant, capsazepine (Tetrahedron, Vol. 53, No. 13, pp. 4791- 4814, 1997) and
olvanil - N-(4-hydroxy-3-methoxybenzyl)oleamide (J. Med. Chem. 1993, 36, 2595-
2604).

20 US 3424760 and US 3424761 both describe a series of 3-Ureidopyrrolidines that
are said to exhibit analgetic, central nervous system, and pyschopharmacologic activities.
These patents specifically disclose the compounds 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl
urea and 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea respectively.

25 International Applications, publication numbers WO02/08221, WO02/16317,
WO02/16318 and WO02/16319 each disclose certain vanilloid receptor antagonists and
their use for the treatment of diseases associated with the activity of vanilloid receptor.

30 A structurally novel class of compounds has now been found which possess
vanilloid receptor (VR1) antagonist activity. They are therefore potentially useful in the
treatment and/or prophylaxis of diseases or disorders mediated by or associated with the
activity of the vanilloid receptor.

The present invention therefore provides, in a first aspect, a compound of formula
(I) or a salt thereof or a solvate thereof:



wherein:

P is phenyl or naphthyl;

R¹ and R² are independently selected from -H, -halo, -CN, -NO₂, -OH, -CF₃, -OCF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, alkyl, cycloalkyl, alkoxy,

5 -O(CH₂)_nNR⁴R⁵, -C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)alkylaryl, -C(O)aryl, -C(O)(CH₂)_nOR⁶, -C(O)(CH₂)_nNR⁴R⁵, -C(O)Oalkyl, -C(O)NR⁴R⁵, -(CH₂)_nC(O)Oalkyl, -(CH₂)_nOC(O)R⁶, -(CH₂)_nOR⁶, -(CH₂)_nNR⁴R⁵, -(CH₂)_nC(O)NR⁴R⁵, -(CH₂)_nN(R⁴)C(O)R⁶, -(CH₂)_nS(O)₂NR⁴R⁵, -(CH₂)_nN(R⁴)S(O)₂R⁶, -ZAr, arylalkyl-, 10 arylalkoxy-, cycloalkylalkyl-, cycloalkylalkoxy-, R⁶S(O)₂C₁₋₆alkyl-, R⁶S(O)₂C₁₋₆alkoxy-, R⁶S(O)₂N(R⁴)-, R⁶C(O)N(R⁴)-, R⁶S(O)₂N(R⁴)C₁₋₆alkyl-, R⁶C(O)N(R⁴)C₁₋₆alkyl- or R⁶C(O)C₁₋₆alkyl;

15 R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵ together with the atoms to which they are attached form an optionally substituted, saturated ring having 3 to 6 atoms optionally comprising a further nitrogen atom and/or a moiety NR⁶;

15 R⁶ is C₁₋₆alkyl or aryl;

n is 0, 1, 2 or 3;

p is 0, 1, 2 or 3 and when p is 2 or 3 the groups R¹ can be the same or different;

q is 0, 1, 2 or 3 and when q is 2 or 3 the groups R² can be the same or different;

r is 1, 2 or 3; and

20 s is 0, 1 or 2;

and provided that the compound of formula (I) is not 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea or 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea.

Suitably a compound of formula (I) excluding 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea and 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea is a compound of formula (I').

Suitable, optionally substituted, saturated 3-6 membered rings include C₃₋₆azacycloalkane, or C₅₋₈ polymethylene rings.

Suitable optional substituents for saturated 3-6 membered rings includes one or more, suitably one, oxo groups

30 One particular C₃₋₆azacycloalkane ring is a C₃₋₆(2-oxo)azacycloalkane ring.

Preferably P is phenyl.

When p is 1, 2 or 3, R¹ is preferably halogen, alkyl (particularly methyl), alkoxy (particularly methoxy), alkylthio (particularly thiomethyl), C(O)alkyl (particularly acetyl), nitro, CF₃, CN or OCF₃.

35 Preferably p is 1 or 2.

Preferably n is 0 or 1, most preferably 0.

When q is 1, 2 or 3, R² is preferably halogen (particularly fluoro or chloro) or alkyl (particularly methyl). Preferably q is 1 or 2. When q is 1, particularly preferred examples are 3-methyl and 3-fluoro. When q is 2, particularly preferred examples are 3,4-difluoro, 3-fluoro-4-methyl and 3-methyl-4-fluoro.

Suitably r and s have values such that they provide a 4 - 7 membered ring.

Preferably r and s have values such that they provide a 5 or 6 membered ring, most preferably a 5 membered ring.

Particular compounds according to this invention include examples E1 - E27 (as 5 shown below) or a salt thereof or a solvate thereof.

Suitable salts include pharmaceutically acceptable salts.

Suitable solvates include pharmaceutically acceptable solvates. Suitable pharmaceutically acceptable salts include acid addition salts.

As indicated the compounds of formula (I) can form acid addition salts. Suitable 10 pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

15 As indicated the compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated.

Suitable solvates include hydrates.

Suitable solvates include pharmaceutically acceptable solvates, such as pharmaceutically acceptable hydrates.

20 This invention includes within its scope stoichiometric solvates, such as hydrates, as well as non-stoichiometric solvates, such as hydrates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different

25 stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

When used herein "alkyl" whether used alone or as part of another group refers to straight chain or branched chain alkyl groups, such as C₁-12alkyl or C₁-6alkyl. A 30 preferred alkyl group is C₁-6alkyl.

When used herein "cycloalkyl" whether used alone or as part of another group refers to single or fused cycloalkyl groups wherein each ring comprises up to 12 carbon atoms, suitably 3 to 6 carbon atoms. A preferred cycloalkyl group is a C₃-6alkyl group.

35 The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

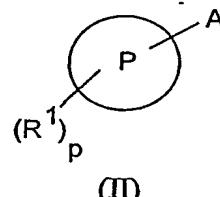
The term 'aryl' is used herein to describe, unless otherwise stated, phenyl or naphthyl.

40 Optional substituents for any aryl group include up to three groups selected from: alkyl, hydroxy, alkyloxy, CN, OCF₃, alkylhalogen, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, mono- or dialkylamino and C(O)alkyl groups.

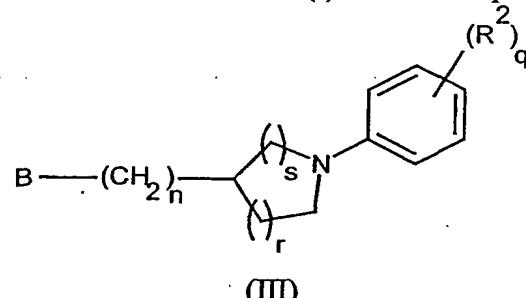
A suitable alkylhalogen group is a CF₃ group.

The term 'naphthyl' is used herein to denote, unless otherwise stated, both naphthalen-1-yl and naphthalen-2-yl groups.

The present invention also provides a process for the preparation of a compound of formula (I') or a salt thereof or a solvate thereof, which process comprises coupling a 5 compound of formula (II):



in which R^1 , P and p are as defined in formula (I) with a compound of formula (III):



10

in which R^2 , n, q, r and s are as defined in formula (I) and A and B contain appropriate functional groups which are capable of reacting together to form the urea moiety; and thereafter, carrying out one or more of the following optional steps:

15 (i) removing any protecting groups
 (ii) converting R^1 into another R^1 or R^2 into another R^2 ; and
 (iii) forming a salt of a compound of formula (I') or a solvate of a compound of formula (I).

Suitable examples of appropriate A and B groups include:

20 (a) A is $-N=C=O$ and B is NH_2 ; or A is NH_2 and B is $N=C=O$ or
 (b) A is NH_2 and B is NH_2 together with an appropriate urea forming agent.

In process (a) or (c), that is when A is $-N=C=O$ and B is NH_2 or vice versa, the reaction is carried out in an inert solvent such as dichloromethane or acetonitrile.

25 In process (b) the reaction is preferably carried out in the presence of an appropriate urea forming agent, such as carbonyl diimidazole or phosgene, a suitable solvent being an inert organic solvent such as dimethylformamide, tetrahydrofuran, or dichloromethane at ambient or elevated temperature optionally in the presence of a base such as triethylamine or pyridine.

30 An alternative method of synthesis of the unsymmetrical urea compounds of formula (I') is from a diaryl carbonate, via the corresponding carbamate. Such a methodology is described by Freer et al. (Synthetic Communications, 26(2), 331 - 349,

1996). It would be appreciated by those skilled in the art that such a methodology could be readily adapted for preparation of the compounds of formula (I).

5 The above mentioned optional process steps (1), (2) or (3) are carried out using the appropriate conventional methods, for example those disclosed in standard reference texts such as *Comprehensive Organic Transformations*, R.C. Larock, Wiley-VCH (Chichester), 1999.

10 It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl, *tert*-butyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures well known in the art.

15 Compounds of formulae (II) and (III) are commercially available, or they may be prepared by procedures described herein, by known methods or by analogous procedures thereto.

20 Salts including pharmaceutically acceptable salts may be prepared by use of appropriate conventional methods, such as treating a compound of formula (I) with an appropriate salting agent, for example the preparation of acid addition salts is conveniently effected by treatment with an appropriate acid or acid derivative.

Solvates including pharmaceutically acceptable solvates may be prepared by use of appropriate conventional methods.

25 As indicated above, the compounds of formula (I) and their pharmaceutically acceptable salts or pharmaceutically acceptable solvates have Vanilloid receptor antagonist (VR1) activity and are believed to be of potential use for the treatment or prophylaxis of certain diseases or disorders mediated or associated with the activity of vanilloid receptor, including disorders such as pain, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, 30 cancer pain, algesia, neuralgia, migraine, neuropathies, diabetic neuropathy, sciatica, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, inflammatory disorders, oesophagitis, gastroesophageal reflux disorder (GERD), irritable bowel syndrome, inflammatory bowel disease, pelvic 35 hypersensitivity, urinary incontinence, cystitis, burns, psoriasis, emesis, stomach duodenal ulcer and pruritus.

40 Thus the invention also provides a compound of formula (I') or a pharmaceutically acceptable salt thereof, for use as an active therapeutic substance, in particular in the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor. In particular the invention provides a compound of

formula (I') or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of pain.

5 The invention further provides a method of treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I')

10 The invention provides for the use of a compound of formula (I') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor.

15 In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. Accordingly, the present invention also provides a pharmaceutical composition, which comprises a compound of formula (I') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier or excipient.

20 A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral, rectal administration or intravesical administration to the bladder and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions, suspensions or suppositories. Orally administrable compositions are generally preferred.

25 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

30 Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

35 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle

instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

5 The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. For systemic administration, dosage levels from 0.01mg to

10 100mg per kilogramme of body weight are useful in the treatment of pain. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20, 20 to 250, or 0.1 to 500.0 mg, for example 0.2 to 5 and 0.1 to 250 mg; and such unit doses may be administered more than once a day, for example two or three times a day, so that the total daily dosage is in the range of about 0.5 to 1000 mg; and such therapy may extend 15 for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

20 The following Descriptions and Examples illustrate the invention but do not limit it in any way.

Description 1**(R)-2-Hydroxymethylpyrrolidine-1-carboxylic acid benzyl ester (D1)**

To a solution of *R*-(*-*)-pyrrolidinemethanol (5g, 0.05mol) and triethylamine (2eq., 14ml) in DCM(30ml) was added dropwise a solution of benzyl chloroformate in DCM (20ml) at 5 ambient temperature. After stirring for 4h the DCM solution was partitioned with water (50ml) and the organic phase separated, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was chromatographed on silica gel eluting with EtOAc to afford a clear oil (9.76g, 81%).

10 Description 2**(R)-2-(*tert*-Butyldimethylsilyloxy)methyl)pyrrolidine-1-carboxylic acid benzyl ester (D2)**

A solution of D1 (9.70g, 0.04mol), imidazole (1.05eq., 2.95g) and *tert*-butyldimethylsilyl chloride (1.1eq., 6.22g) in DMF (dry, 50ml) was stirred overnight at ambient temperature. 15 Solvent was removed under reduced pressure and the residue partitioned between Et₂O and water. The aqueous phase was separated and the organic phase washed with dilute HCl (0.5M, 2x100ml), followed by water (2x100ml) and the organic phase was then dried (anhydrous MgSO₄), filtered and concentrated under reduced pressure to afford an oil (12.70g). This was used in the next step without purification.

20

Description 3**(R)-2-(*tert*-Butyldimethylsilyloxy)methyl)pyrrolidine (D3)**

To a solution of D2 (12.7g, 0.036mol) and cyclohexene (excess, 20ml) in ethanol (100ml) was added 10% palladium on charcoal catalyst. Reaction was heated at reflux overnight 25 and cooled. Catalyst was filtered and the filtrate concentrated to leave an oil (6.69g) which was used in the next step without purification.

Description 4**(R)-2-(*tert*-Butyldimethylsilyloxy)methyl)-1-(3-methylphenyl)pyrrolidine (D4)**

A suspension of cesium carbonate (1.5eq., 15.2g), palladium acetate (10mol%, 0.69g) and BINAP (15mol%, 2.90g) in 1,4-dioxane (dry, 50ml) was sonicated for 45 min. To the 30 resulting dark pink suspension was added a solution of D3 (6.60g, 0.03mol) and 3-bromotoluene (2eq., 10.60g) in 1,4-dioxane (dry, 30ml). The reaction was heated at 100C for 18h and cooled. Solvent was removed under reduced pressure and the residue 35 partitioned between DCM and water. Organic phase was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to leave an oil. Chromatography on silica gel eluting with EtOAc in hexane (gradient elution, maximum 5%) afforded the product as an oil (7.24g, 77%).

40 Description 5**((R)-1-(3-Methylphenyl)pyrrolidin-2-yl)methanol (D5)**

5 A solution of D4 (7.20g, 0.024mol) in THF (50ml) was treated with tetrabutylammonium fluoride (1M solution in THF, 2eq., 96ml) and then stirred at ambient temperature for 18h. Solvent was removed under reduced pressure and residue chromatographed on silica gel eluting with EtOAc in hexane (gradient elution, maximum 50%) to afford the product as an oil (3.70g, 81%).

Description 6

2-((R)-1-(3-Methylphenyl)pyrrolidin-2-ylmethyl)isoindole-1,3-dione (D6)

10 To a suspension of phthalimide (1.1eq., 3.14g), triphenylphosphine (1.1eq., 5.59g) and D5 (3.70g, 0.019mol) in THF (50ml) was added dropwise diisopropyl azodicarboxylate (1.1eq., 4.20ml). Reaction was stirred for 18h at ambient temperature and then solvent removed under pressure. The crude product was chromatographed on silica gel eluting with EtOAc in hexane (gradient elution, maximum 10%) to afford the product as an oil (5.89, 95%).

15

Description 7

((R)-1-(3-Methylphenyl)pyrrolidin-2-yl)methylamine (D7)

20 A solution of D6 (5.80g, 0.018mol) in ethanol (60ml) and hydrazine hydrate (2.eq., 2ml) was heated at reflux for 1h and cooled. The resulting precipitate was filtered and filtrate concentrated under reduced pressure to leave an oil. Chromatography on silica gel eluting with methanol in DCM (gradient elution, maximum 10%) afforded the product as an oil (3.58g, 94%).

Description 8

25 **(S)-2-Hydroxymethylpyrrolidine-1-carboxylic acid benzyl ester (D8)**

The title compound was prepared from (S)-(+)-2-pyrrolidinemethanol using the procedure outlined for Description 1 (10.21g, 92%).

Description 9

30 **(S)-2-(tert-Butyldimethylsilyloxyethyl)pyrrolidine-1-carboxylic acid benzyl ester (D9)**

The title compound was prepared from D8 using the procedure outlined for Description 2 (14.93, 99%).

35 **Description 10**

(S)-2-(tert-Butyldimethylsilyloxyethyl)pyrrolidine (D10)

The title compound was prepared from D9 using the procedure outlined for Description 3 (7.69g, 83%).

40 **Description 11**

(S)-2-(tert-Butyldimethylsilyloxyethyl)-1-(3-methylphenyl)pyrrolidine (D11)

The title compound was prepared from D10 using the procedure outlined for Description 4 (2.74g, 50%).

Description 12

5 **((S)-1-(3-Methylphenyl)pyrrolidin-2-yl)methanol (D12)**

The title compound was prepared from D11 using the procedure outlined for Description 5 (1.57g, 95%).

Description 13

10 **2-((S)-1-(3-Methylphenyl)pyrrolidin-2-ylmethyl)isoindole-1,3-dione (D13)**

The title compound was prepared from D12 using the procedure outlined for Description 6 (2.27g, 87%).

Description 14

15 **((S)-1-(3-Methylphenyl)pyrrolidin-2-yl)methylamine (D14)**

The desired product was prepared from D13 using the procedure outlined for Description 7 (1.06g, 82%).

Description 15

20 **(S)-1-((3-Methylphenyl)pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (D15)**

The title compound was prepared from (3*S*)-(-)-3-(*tert*-butyloxycarbonylamino)pyrrolidine (TCI, Japan) and 3-bromotoluene using the procedure outlined for Description 4 (2.15g, 60%).

25 **Description 16**

(S)-1-(3-Methylphenyl)pyrrolidin-3-ylamine (D16)

A solution of D15 (2.10g, 7.6mmol) in DCM (20ml) and trifluoroacetic acid (5eq., 2.9ml) was heated at 40°C for 18h and cooled. The reaction was then partitioned with aqueous sodium hydrogen carbonate (10%, 50ml) and the organic phase separated. Addition of anhydrous MgSO₄ followed by filtration and concentration of filtrate under reduced pressure afforded the crude product. Bulb to bulb distillation under reduced pressure afforded the product as a clear oil (0.89g, 68%).

Description 17

35 **(R)-1-((3-Methylphenyl)pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (D17)**

The title compound was prepared from 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine (TCI, Japan) and 3-bromotoluene using the procedure outlined in Description 4 (2.08g, 58%).

40 **Description 18**

(R)-1-(3-Methylphenyl)pyrrolidin-3-ylamine (D18)

The title compound was prepared from D17 using the procedure outlined for Description 16 and the isolated product was used without purification (1.03g, 78%).

Description 19

5 **(R)-1-((3-Fluorophenyl)pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (D19)**

The title compound was prepared from 3*R*-(+)-3-(*tert*-butyloxycarbonylamino) pyrrolidine (TCI, Japan) and 1-bromo-3-fluorotoluene using the procedure outlined in Description 4 (3.20g, 88%).

10 **Description 20**

(R)-1-(3-Fluorophenyl)pyrrolidin-3-ylamine (D20)

The title compound was prepared from D19 using the procedure outlined for Description 16 (1.68g, 85%).

15 **Description 21**

(R)-1-((3-Fluoro-4-methylphenyl)pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (D21)

The title compound was prepared from 3*R*-(+)-3-(*tert*-butyloxycarbonylamino) pyrrolidine (TCI, Japan) and 2-fluoro-4-bromotoluene using the procedure outlined in Description 4 (25.40g, 62%).

20

Description 22

(R)-1-(3-Fluoro-4-methylphenyl)pyrrolidin-3-ylamine (D22)

The title compound was prepared from D21 using the procedure outlined for Description 16 (5.40g, 85%).

25

Description 23

(R)-1-((3,4-Difluorophenyl)pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (D23)

The title compound was prepared from 3*R*-(+)-3-(*tert*-butyloxycarbonylamino) pyrrolidine (TCI, Japan) and 4-bromo-1,2-fluorobenzene using the procedure outlined in Description 4 (11.20g, 78%).

Description 24

(R)-1-(3,4-Difluorophenyl)pyrrolidin-3-ylamine (D24)

The title compound was prepared from D23 using the procedure outlined for Description 16 (6.40g, 77%).

Description 25

(R)-1-((4-Fluoro-3-methylphenyl)pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (D25)

The title compound was prepared from 3*R*-(+)-3-(*tert*-butyloxycarbonylamino) pyrrolidine (TCI, Japan) and 5-bromo-2-fluorotoluene using the procedure outlined in Description 4 (0.25g, 31%).

Description 26**(R)-1-((4-Fluoro-3-methylphenyl)pyrrolidin-3-yl)amine (D26)**

The title compound was prepared from D25 using the procedure outlined for Description 16 (0.14g, 91%).

5

Description 27**(S)-1-((3-Fluorophenyl)pyrrolidin-3-yl)carbamic acid *tert*-butyl ester (D27)**

The title compound was prepared from 3*S*-(-)-3-(*tert*-butyloxycarbonylamino)pyrrolidine (TCI, Japan) and 1-bromo-3-fluorotoluene using the procedure outlined in Description 4 (0.17g, 55%).

10

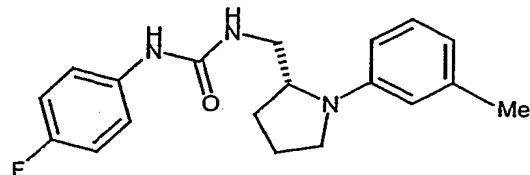
Description 28**(S)-1-(3-Fluorophenyl)pyrrolidin-3-ylamine (D28)**

The title compound was prepared from D26 using the procedure outlined for Description 16 (0.078g, 71%).

15

Example 1***N*-(4-Fluorophenyl)-*N'*-[(*R*)-1-((3-methylphenyl)pyrrolidin-2-ylmethyl)]urea (E1)**

20



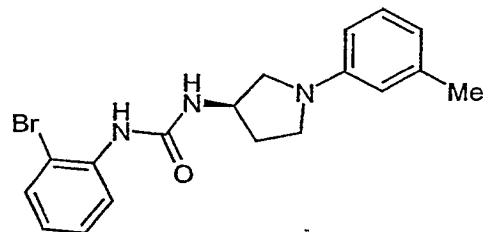
25

To a solution of ((*R*)-1-(3-methylphenyl)pyrrolidin-2-yl)methylamine (D7, 0.1g, 0.5mmol) in DCM was added 4-fluorophenyl isocyanate (0.072g, 0.5mmol). Reaction was stirred at ambient temperature for 1h and then concentrated under reduced pressure. Chromatography of the residual oil on silica gel eluting with methanol and DCM (gradient elution, 3% maximum) afforded the title compound as a white solid (0.12g, 73%).

¹H NMR (400MHz, CDCl₃) δ 7.15-7.10 (m, 3H), 6.96 (m, 2H), 6.56 (m, 3H), 6.40 (br, 1H), 4.77 (br, 1H), 3.95 (br, 1H), 3.47 (m, 1H), 3.37 (m, 2H), 3.15 (m, 1H), 2.30 (s, 3H), 2.00-1.87 (m, 4H). MH⁺ 328

30

Example 2***N*-(2-Bromophenyl)-*N'*-[(*R*)-1-(3-methylphenyl)pyrrolidin-3-yl]urea (E2)**



The title compound was prepared from D18 and 2-bromophenyl isocyanate using the procedure outlined for Example 1 (0.12g, 58%).

¹H NMR (250MHz, CDCl₃) δ 8.07 (d, 1H), 7.50 (d, 1H), 7.27 (m, 1H), 7.14 (m, 1H), 6.99 (m, 1H), 6.72 (br, 1H), 6.57 (m, 1H), 6.40 (m, 2H), 4.99 (d, 1H), 4.56 (br, 1H), 3.55 (m, 1H) 3.45 (m, 1H), 3.37-3.23 (m, 2H), 2.31 (m, 4H) 2.04 (m, 1H). MH⁺ 374, 376.

10 The following Examples were prepared using a similar procedures to those disclosed herein and in particular those disclosed for E1 using the appropriate amine and isocyanate.

| Example | Amine | MH^+ |
|--|-------|----------|
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea (E3) | D7 | 388, 390 |
| <i>N</i> -(4-Fluorophenyl)- <i>N'</i> -[((<i>S</i>)-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea (E4) | D14 | 328 |
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>S</i>)-1-(3-methylphenyl)pyrrolidin-2-ylmethyl)]urea (E5) | D14 | 388, 390 |
| <i>N</i> -(4-Fluorophenyl)- <i>N'</i> -[((<i>S</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E6) | D16 | 314 |
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>S</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E7) | D16 | 374, 376 |
| <i>N</i> -(4-Fluorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E8) | D18 | 314 |
| <i>N</i> -(4-Fluorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea (E9) | D20 | 317 |
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea (E10) | D20 | 378, 380 |
| <i>N</i> -(1-Naphthyl)- <i>N'</i> -[((<i>R</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E11) | D18 | 346 |
| <i>N</i> -(2,3-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E12) | D18 | 364, 367 |
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>S</i>)-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea (E13) | D28 | 378, 380 |

| | | |
|---|-----|----------|
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>R</i>)-1-(4-fluoro-3-methylphenyl)pyrrolidin-3-yl)]urea (E14) | D26 | 392, 394 |
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea (E15) | D24 | 396, 398 |
| <i>N</i> -(2-Bromophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea (E16) | D22 | 392, 394 |
| <i>N</i> -(3-Chloro-2-methylphenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E17) | D18 | 343, 345 |
| <i>N</i> -(2,3-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E18) | D18 | 366, 368 |
| <i>N</i> -(2,5-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-methylphenyl)pyrrolidin-3-yl)]urea (E19) | D18 | 366, 368 |
| <i>N</i> -(2,3-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea (E20) | D20 | 369, 371 |
| <i>N</i> -(2,5-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea (E21) | D20 | 369, 371 |
| <i>N</i> -(3-Chloro-2-methylphenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluorophenyl)pyrrolidin-3-yl)]urea (E22) | D20 | 348, 350 |
| <i>N</i> -(3-Chloro-2-methylphenyl)- <i>N'</i> -[((<i>R</i>)-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea (E23) | D24 | 367, 369 |
| <i>N</i> -(2,3-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea (E24) | D24 | 388, 390 |
| <i>N</i> -(2,5-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3,4-difluorophenyl)pyrrolidin-3-yl)]urea (E25) | D24 | 388, 390 |
| <i>N</i> -(3-Chloro-2-methylphenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea (E26) | D22 | 362, 364 |
| <i>N</i> -(2,3-Dichlorophenyl)- <i>N'</i> -[((<i>R</i>)-1-(3-fluoro-4-methylphenyl)pyrrolidin-3-yl)]urea (E27) | D22 | 383, 385 |

Pharmacological Data

As referenced above, the compounds of this invention are vanilloid receptor (VR1) antagonists and hence have useful pharmaceutical properties. Vanilloid receptor (VR1) antagonist activity can be determined and demonstrated for any particular compound by use of conventional methods, for example those disclosed in standard reference texts such as D. Le Bars, M. Gozarin and S. W. Cadden, Pharmacological Reviews, 2001, 53(4), 597-652] or such other texts mentioned herein. The screen used for the compounds of this invention was derived from a FLIPR based calcium assay, similar to that described by Smart et al. (British Journal of Pharmacology, 2000, 129, 227-230).

Transfected astrocytoma 1321N1 cells, stably expressing human VR1, were seeded into FLIPR plates at 25,000cells/well (96-well plate) and cultured overnight.

The cells were subsequently loaded in medium containing 4 μ M Fluo-3 AM (Molecular Probes) for 2 hours, at room temperature, in the dark. The plates were then washed 4 times with Tyrode containing 1.5mM calcium, without probenecid.

The cells were pre-incubated with compound or buffer control at room

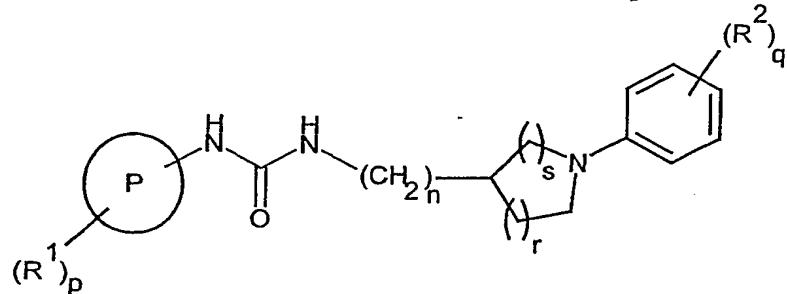
5 temperature for 30 minutes. Capsaicin (Sigma) was then added to the cells. Compounds having antagonist activity against the human VR1 were identified by detecting differences in fluorescence when measured after capsaicin addition, compared with no compound buffer controls. Thus, for example, in the buffer control capsaicin addition results in an increase in intracellular calcium resulting in fluorescence. A compound having

10 antagonist activity blocks the capsaicin binding to the receptor, there is no signalling and therefore no increase in intracellular calcium levels and consequently lower fluorescence. pK_b values are generated from the IC₅₀ values using the Cheng-Prusoff equation.

All compounds tested by the above methodology have pK_b > 6.0 The preferred compounds have pK_b > 7.0.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

5 P is phenyl or naphthyl;

R¹ and R² are independently selected from -H, -halo, -CN, -NO₂, -OH, -CF₃, -OCF₃, -NR⁴R⁵, -S(O)_mR⁶, -S(O)₂NR⁴R⁵, -OS(O)₂R⁶, -OS(O)₂CF₃, alkyl, cycloalkyl, alkoxy, -O(CH₂)_nNR⁴R⁵, -C(O)CF₃, -C(O)alkyl, -C(O)cycloalkyl, -C(O)alkylaryl, -C(O)aryl,

10 -C(O)(CH₂)_nOR⁶, -C(O)(CH₂)_nNR⁴R⁵, -C(O)Oalkyl, -C(O)NR⁴R⁵, -(CH₂)_nC(O)Oalkyl, -(CH₂)_nOC(O)R⁶, -(CH₂)_nOR⁶, -(CH₂)_nNR⁴R⁵, -(CH₂)_nC(O)NR⁴R⁵, -(CH₂)_nN(R⁴)C(O)R⁶, -(CH₂)_nS(O)₂NR⁴R⁵, -(CH₂)_nN(R⁴)S(O)₂R⁶, -ZAr, arylalkyl-, arylalkoxy-, cycloalkylalkyl-, cycloalkylalkoxy-, R⁶S(O)₂C₁₋₆alkyl-, R⁶S(O)₂C₁₋₆alkoxy-, R⁶S(O)₂N(R⁴)-, R⁶C(O)N(R⁴)-, R⁶S(O)₂N(R⁴)C₁₋₆alkyl-, R⁶C(O)N(R⁴)C₁₋₆alkyl- or

15 R₆C(O)C₁₋₆alkyl;

R⁴ and R⁵ may be the same or different and represent H or alkyl or R⁴ and R⁵ together with the atoms to which they are attached form an optionally substituted, saturated ring having 3 to 6 atoms optionally comprising a further nitrogen atom and/or a moiety NR⁶;

R⁶ is C₁₋₆alkyl or aryl;

20 n is 0, 1, 2 or 3;

p is 0, 1, 2 or 3 and when p is 2 or 3 the groups R¹ can be the same or different;

q is 0, 1, 2 or 3 and when q is 2 or 3 the groups R² can be the same or different;

r is 1, 2 or 3; and

s is 0, 1 or 2;

25 and provided that the compound of formula (I) is not 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea or 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea.

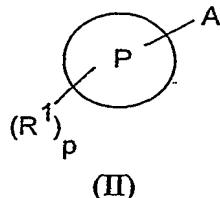
2. A compound according to claim 1 in which P is phenyl.

30 3. A compound according to claim 1 or claim 2 in which n is 0 or 1.

4. A compound according to claim 1 which is compound Example E1 - E16 or a pharmaceutically acceptable salt thereof.

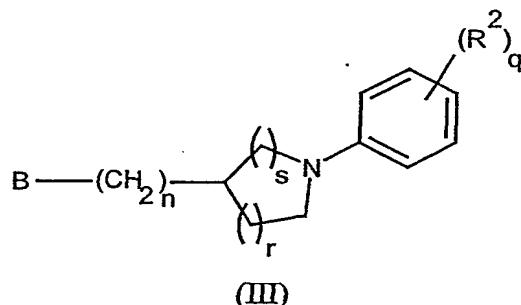
5. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises coupling a compound of formula (II):

5



in which R^1 , P and p are as defined in formula (I) with a compound of formula (III):

10



in which R^2 , n, q, r and s are as defined in formula (I) and A and B contain appropriate functional groups which are capable of reacting together to form the urea moiety; and thereafter, carrying out one or more of the following optional steps:

- (i) removing any protecting groups
- 15 (ii) converting R^1 into another R^1 or R^2 into another R^2 ; and
- (iii) forming a salt of a compound of formula (I) or a solvate of a compound of formula (I).

20

6. A compound according to any one of claims 1 to 4 for use in therapy.

7. A compound according to any one of claims 1 to 4 for use in the treatment of pain.

8. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier or excipient.

30

9. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor

10. A method for the treatment or prophylaxis of diseases or disorders mediated or associated with the activity of vanilloid receptor, which comprises administering a non toxic, therapeutically effective amount to a patient in need thereof of

a compound of formula (I') or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/04802

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D207/09 C07D207/14 A61K31/402

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | PAN P-C ET AL: "Soluble Polymer-Supported Synthesis of Arylpiperazines" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9505-9508, XP004144238 ISSN: 0040-4039 see page 9506, compound 10 with R is group C --- | 1-4 |
| X | US 3 424 760 A (HELSLEY, GROVER C. ET AL) 28 January 1969 (1969-01-28) column 4; example 3 column 1, line 45 - line 54 --- -/- | 1-10 |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

| | |
|---|--|
| Date of the actual completion of the international search | Date of mailing of the international search report |
| 13 August 2002 | 25/09/2002 |

Name and mailing address of the ISA
 European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Bérillon, L

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 02/04802

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X | US 3 424 761 A (HELSLEY, GROVER C. ET AL) 28 January 1969 (1969-01-28) column 5; example 8 column 1, line 43 - line 51 ---- | 1-10 |
| A | HESLEY ET AL.: "Synthesis and biological activity of some 1-substituted 3-pyrrolidinylureas" JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, no. 5, 1968, pages 1034-1037, XP001095126 see table III, compounds 38 and 40 ----- | 1-10 |

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 02/04802

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/04802

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|-------------------------|------------------|
| US 3424760 | A 28-01-1969 | NONE | |
| US 3424761 | A 28-01-1969 | GB 1172033 A | 26-11-1969 |

THIS PAGE BLANK (USPTO)